Claim 9	claim 2; page 5, lines 14-15; page 12, lines 17-21
Claims 10-11	claims 3-4; page 4, lines 13-23; page 5, lines 17-20; page 7, line 23 - page 10, line 22
Claim 12	claim 5; page 5, lines 21-23; page 12, line 22 - page 13, line 2
Claim 13	page 4, lines 28-29; page 11, lines 19-26
Claim 14	page 4, lines 28-29; page 11, lines 26-28
Claim 15	page 4, lines 29-30; page 11, lines 13-16; page 15, lines 1-3
Claim 16	page 5, line 1; page 11, lines 16-17
Claim 17	page 3, lines 25-27; page 4, lines 24-25; page 11, lines 19-26
Claim 18	page 9, line 16 to page 10, line 22
Claims 20-21	page 7, line 23 to page 10, line 22
Claims 22-24	claim 6; page 5, lines 26-29; page 7, lines 23-25; page 12, lines 25-28
Claims 25-26	claim 6; page 4, lines 7-8; page 12, line 28 - page 13, line 1; page 29, line 16 - page 32, line 3
Claim 27	claim 6; page 4, lines 8-9; page 13, lines 1-2; page 32, line 6 - page 33, line 19
Claims 28-29	page 5, lines 5-9; page 26, lines 11-16; page 28, lines 27-29

As required, attached hereto as **Appendix A** is a marked-up version of the changes made to the claims by this Amendment. For the Examiner's convenience, also attached hereto is an **Appendix B** showing all pending claims as amended remaining in this application.

Oath/Declaration

The undersigned held a telephone interview with the Examiner on December 30, 2002 with reference to the Oath/Declaration for the present application. During the interview, the Examiner acknowledged that the USPTO records for priority application U.S. Serial No. 08/196,043 ("the '043 application") were in error and that the '043 application was indeed filed on February 11, 1994. The Examiner also confirmed that a request to correct the filing receipt (and hence the USPTO records) for the '043 application was filed by Applicant on December 27, 1999 but was never processed. The Examiner further indicated that the request had now been

processed and that a corrected filing receipt would be issued in due course for the '043 application and the present application. Applicant has since received a corrected filing receipt for the '043 application; however, Applicant has yet to receive a corrected filing receipt for the present application and respectfully requests that one be issued.

Specification

Pages 24 and 25 have been replaced with substitute pages 24a, 24b, 25a, and 25b that include larger versions of the chemical structures. The larger versions are identical to the originals expect for their size. No change in content results from this change in size. Applicant respectfully submits that this amendment overcomes the Examiner's objection to pages 24 and 25.

Claim objections

Claim 4 has been canceled, accordingly the Examiner's objection to claim 4 is moot. Applicant further notes that new claim 11 (that parallels canceled claim 4) includes longer terms that supplement the art-recognized abbreviations that were objected to in canceled claim 4.

Claim rejections under 35 U.S.C. §112

Rejection of claims 1-7 for lacking written description

Claims 1-7 have been rejected as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventor(s), at the time the application was filed, were in possession of the claimed invention. Claim 1-7 have been canceled, accordingly the rejection is moot. Further, Applicant respectfully traverses this rejection as applied to new claims 8-29.

The present specification (see, for example page 13, line 4 - page 15, line 3; see also page 19, line 10 - page 21, line 19) makes perfectly clear that the invention encompasses methods for preparing *any* oligomerizing agent that includes two covalently linked non-peptidic moieties each of which binds to the same or a different protein mediator (e.g., a cell surface receptors), as required to describe the broadest of the new claims (e.g., claims 8, 9, 12 and 19-21). The specification also specifically recites relevant subsets of cell surface receptors that can act as protein mediators as recited in claims 10, 11 and 18 (see, for example, page 3, line 27 - page 4,

line 9; page 4, lines 19-23; page 5, lines 17-20; page 7, line 22 - page 10, line 23). Likewise, the specification specifically points to dimerizing agents having the characteristics recited in new claims 13-17 (see, for example, page 11, line 13 - page 12, line 14); describes the specific biological events that are recited in claims 22-27 (see, for example, page 4, lines 7-9; page 5, lines 26-29; page 7, lines 23-25; page 12, line 25 - page 13, line 2; page 29, line 16 - page 33, line 19); and describes the pharmaceutical compositions that are recited in new claims 28 and 29 (see, for example, page 28, lines 21-29). The present specification and claims as originally filed clearly put the public on notice that the inventors considered the present claims to be within the scope of their invention.

Furthermore, those skilled in the art would have fully appreciated and understood the provided description as properly defining the invention. In particular, they would have appreciated that moieties having a wide variety of chemical structure may be used as components of oligomerizing agents for use in accordance with the present invention.

In fact, long after the effective date of the present claims, and after the publication of Applicant's corresponding PCT application Serial No. US95/14177, other researchers began to recognize that small, non-peptidic agents can be used to dimerize signal transduction components (see, for example, Qureshi et al., *Proc. Natl. Acad. Sci. USA* 96:12156, 1999 attached hereto as **Exhibit A** and Tian et al., *Science* 281:257, 1998 attached hereto as **Exhibit B**). These researchers immediately recognized that their observations of a single dimerization event were broadly generalizable. For example, researchers at Ligand Pharmaceuticals and SmithKline Beecham showed that a non-peptidic small molecule can dimerize the granulocyte-colony-stimulating factor receptor and concluded:

> "Our findings indicate that a small molecule can trigger the activation of a large (~120 kD) receptor protein that requires dimerization for activation, through a domain not involved in binding the natural ligand." (Tian et al., last sentence, page 259).

Similarly, researchers at Merck showed that a non-peptidic small molecule can dimerize the erythropoietin receptor and concluded:

"...it does validate the concept that the EPOR, and by extension most cytokine receptors, can be ligated together in an active conformation by a nonpeptidyl molecule. The only requirement is that the small molecule must be able to interact with both chains of the receptor. This paper also lays out a basic strategy for identifying cytokine mimetics by converting an antagonist into an agonist." (Qureshi et al., last sentence, page 12161).

Against the backdrop of real-life conclusions and expectations made by Qureshi et al. and Tian et al., and in view of the nature and broad applicability of the claimed invention, an overly rigid search for structure-function disclosure misses the mark. Providing or finding moieties that bind to a protein is a given here. Linking these together to produce a dimerizing agent is also a given. It is and was within the level of the skilled artisan. The fact that those actual practitioners in this art relied upon the same sort of language as Applicant makes it plain that, at least in this art, Applicant's language is and was reasonably, appropriately and sufficiently descriptive to put the public on notice of Applicant's possession of the invention. Requiring Applicant to use language other than that which is reasonable in their art cannot be consistent with the intent or effect of the description requirement.

The present specification provides sufficient description concerning the identification of those moieties whose use fall within the scope of the present claims; further description is neither necessary nor appropriate. Withdrawal of the rejection is respectfully requested.

Rejection of claims 1-7 for being indefinite

Claims 1-7 have been canceled, accordingly the Examiner's rejection is moot. Applicant further notes that new claims 8 and 19 (that parallel canceled claim 1 and further dependent claims 13-14, 22, and 25-27) recite the terms "that effects" and "that binds" instead of "capable of effecting" and "capable of binding". As noted by the Examiner, the use of this language overcomes the Examiner's indefiniteness rejection under 35 U.S.C. §112, second paragraph.

Claim rejections under 35 U.S.C. §102

Rejections of claims 1-6 over Rodbard, Willey, Feuillolet, Engel and Heidaran

Claims 1-4 have been rejected under 35 U.S.C. §102(b) over U.S. Patent No. 4,468,383 to Rodbard ("Rodbard") or Willey et al., Diabetologia 15:281, 1978 ("Willey"). Claims 1-3 have

been rejected under 35 U.S.C. §102(b) over Feuillolet et al., J. Steroid Biochem. 35:583, 1990 ("Feuillolet"). Claims 1, 2, 5 and 6 have been rejected under 35 U.S.C. §102(b) over Engel et al., Biochemistry 30:3161, 1991 ("Engel"). Claims 1-3, 5 and 6 have been rejected under 35 U.S.C. §102(b) over Heidaran et al., J. Biol. Chem. 266:20232, 1991 ("Heidaran"). Claim 1-6 have been canceled, accordingly the rejection is moot. Further, Applicant respectfully traverses this rejection as applied to new claims 8-29.

As noted by the Examiner, Rodbard, Willey, Feuillolet, Engel and Heidaran describe the preparation of *peptidic* agents for dimerizing receptors. In general, these are prepared by covalently linking two peptides that have been derived from a natural peptide ligand of a given receptor (e.g., enkephalins, insulin, ACTH, PDGF-A/-B, etc.). The teachings of these references cannot anticipate the claimed invention. Claims 8 and 19 (and claims 9-18 and 20-24 that depend therefrom) are drawn to a method for preparing an agent that effects biological events mediated by association of two or more endogenous protein mediators including cell surface receptors. The dimerizing agent includes a first *non-peptidic* moiety that binds to one of the protein mediators covalently linked with a second *non-peptidic* moiety that binds to the other protein mediator. The teachings of Rodbard, Willey, Feuillolet, Engel and Heidaran are limited to methods for preparing dimerizing agents that include *peptidic* entities. The cited references fail to teach or suggest a method for preparing *any* dimerizing agent that includes a *non-peptidic* moiety that binds to a protein mediator. A rejection for lack of novelty is proper only if each and every element of the claim is taught by the cited reference. Accordingly, Applicant respectfully submits that the cited references cannot anticipate new claims 8-29.

Rejection of claims 1-3 and 7 over Kao

Claims 1-3 and 7 have been rejected under 35 U.S.C. §102(e) over U.S. Patent No. 5,120,727 to Kao et al. ("Kao"). Claim 1-3 and 7 have been canceled, accordingly the rejection is moot. Further, Applicant respectfully traverses this rejection as applied to new claims 8-29.

As noted by the Examiner, Kao describes a method that involves covalently linking two identical rapamycin monomers. Rapamycin binds a cytoplasmic protein called FKBP (FK506 binding protein, see Bierer et al., *Proc. Natl. Acad. Sci. USA* 87:9231, 1990 attached hereto as **Exhibit C**). When associated with FKBP, rapamycin also binds another cytoplasmic protein called FRAP (FKBP-rapamycin-associated protein, see Brown et al., *Nature* 369:756, 1994

attached hereto as **Exhibit D**). The teachings of this reference cannot anticipate the claimed invention. Claim 8 (and claims 9-18 that depend therefrom) are drawn to a method for preparing an agent that effects biological events mediated by association of two or more endogenous *cell surface receptors*. The dimerizing agent includes a first non-peptidic moiety that binds to one of the *cell surface receptors* covalently linked with a second non-peptidic moiety that binds to the other *cell surface receptor*. The teachings of Kao are limited to a specific agent that includes two covalently linked rapamycin monomers. As noted above, these rapamycin monomers bind to *cytoplasmic proteins* and not to cell surface receptors as claimed. Kao fails to teach or suggest a method for preparing *any* dimerizing agent that includes a non-peptidic moiety that binds to a *cell surface receptor*. A rejection for lack of novelty is proper only if each and every element of the claim is taught by the cited reference. Accordingly, Applicant respectfully submits that Kao cannot anticipate claim 8 (and claims 9-18 that depend therefrom).

Applicant further notes that new claim 19 (and claims 20-26 that depend therefrom) is drawn to a method for preparing an agent that effects biological events mediated by association of two or more *different* endogenous protein mediators. Further, the dimerizing agent includes two *different* non-peptidic moieties. The teachings of Kao are limited to a specific agent that includes two *identical* rapamycin monomers. The cited references fail to teach or suggest a method for preparing *any* dimerizing agent that includes two *different* non-peptidic moieties. A rejection for lack of novelty is proper only if each and every element of the claim is taught by the cited reference. Applicant therefore further submits that Kao cannot anticipate claim 19 (or claims 9-18 that depend therefrom).

Conclusion

For the reasons presented above, it is submitted that the amended and new claims are allowable over the art of record. A check is enclosed in the amount of $36.00 to cover the extra claim fee as follows:

	CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA	RATE	ADDITIONAL FEES
TOTAL CLAIMS	24	MINUS	20	= 4	$9	$36
INDEP. CLAIMS	2	MINUS	3	= 0	$42	0
FIRST PRESENTATION OF A MULTIPLE DEPENDENT CLAIM?				NO	$280	0
TOTAL EXTRA CLAIM FEE FOR THIS AMENDMENT						$36

A check is also enclosed in the amount of $465.00 to cover the Small Entity Fee for the Petition for Extension of Time under 37 C.F.R. §1.136. Please charge any other fees that may be associated with this filing, or credit any overpayment, to our Deposit Account No. 03-1721.

Respectfully submitted,

Charles Lyon, Ph.D.
Agent for Applicant
Limited Recognition Under 37 CFR §10.9(b)

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Dated: April 1, 2003

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I certify that this correspondence is being deposited with the United States Postal Service with sufficient postage as First Class Mail in an envelope addressed to Assistant Commissioner for Patents, Washington, DC 20231.

April 1, 2003 — Linda M. Amato
Date — Signature

Linda M. Amato
Typed or Printed Name of person signing certificate

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APPENDIX A

VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the specification

Original pages 24 and 25 have been **replaced** with substitute pages 24a, 24b, 25a, and 25b.

In the claims

Claims 1-7 have been **canceled** and new claims 8-29 have been **added**.